EXHIBIT 2

trials as a component of vaccines to boost protective cell-mediated immune responses.

Interleukin-15

Interleukin-15 is a 17 kD polypeptide cytokine released by mononuclear phagocytes and certain tissue cells in response to viral infection, LPS, or other signals that trigger innate immunity. Structurally, IL-15 is homologous to IL-2 and signals through the low affinity receptor complex used by IL-2, which will be discussed later in the chapter (see also Box 12–1). The binding of IL-15 to this low affinity IL-2 receptor is markedly increased by interaction with a non-signaling IL-15 binding polypeptide, called the IL-15Rα chain. The IL-15Rα chain is structurally homologous to the IL-2Rα chain, but it does not bind IL-2.

The primary function of IL-15 appears to be to promote the proliferation of NK cells. Since IL-15 is synthesized early in response to viral infections, it may mediate expansion of NK cells within the first 24 to 72 hours of viral infection. IL-15 may also act as a T cell growth factor because it binds and signals through the low affinity IL-2R, which is found on resting T cells. However, it is not known whether enough IL-15 is produced during an infection to signal through this low affinity receptor, nor is it clear whether T cells acquire IL-15Rα.

Tumor Necrosis Factor

Tumor necrosis factor (TNF) *is the principal mediator of the response to gram-negative bacteria* and may also play a role in innate immune responses to other infectious organisms. (Some investigators refer to TNF as TNF-α for historical reasons; we shall use the simpler term throughout this book). TNF was originally identified (and was so named) as a mediator of tumor necrosis that was present in the serum of animals treated with LPS. At low concentrations, LPS stimulates the functions of mononuclear phagocytes and (in mice) acts as a polyclonal activator of B cells (see Chapters 9 and 13), host responses that contribute to elimination of the invading bacteria. However, high concentrations of LPS cause tissue injury, disseminated (widespread) intravascular coagulation (DIC), and shock, often resulting in death. The Shwartzman reaction is an experimental model for studying the pathologic effects of LPS (Box 12–3). It is now clear that TNF is one of the principal mediators of these effects of LPS.

The major cellular source of TNF is the LPS-activated mononuclear phagocyte, although antigen-stimulated T cells, activated NK cells, and activated mast cells can also secrete this protein. IFN-γ, produced by T cells, augments TNF synthesis by LPS-stimulated mononuclear phagocytes. Thus, TNF is a mediator of both innate and specific immunity and an important link between specific immune responses and acute inflammation.

BOX 12–3. The Shwartzman Reaction

The mechanism of lipopolysaccharide (LPS)–mediated tissue injury was investigated by Shwartzman, who found that two intravenous injections of a sublethal quantity of LPS, administered 24 hours apart, would cause disseminated intravascular coagulation (DIC) in the rabbit. This is called the systemic Shwartzman reaction and is due to widespread intravascular thrombus formation on the surfaces of endothelial cells. If the first LPS injection is given intradermally, the second intravenous injection causes hemorrhagic necrosis of skin exclusively at the intradermal injection site. In this localized Shwartzman reaction, tissue injury is caused by activated neutrophils and by inadequate perfusion of the tissue. The inadequate tissue perfusion results from local intravascular coagulation (fibrin formation) and from cellular plugging of the microcirculation by aggregates of neutrophils and platelets. Recent studies have shown that tumor necrosis factor (TNF) can in large part substitute for LPS in eliciting both the local Shwartzman reaction and the systemic toxicity of LPS. Moreover, neutralizing antibody to TNF affords protection against both the injurious and the lethal effects of LPS. Thus, TNF is thought to be an obligatory mediator of LPS-induced tissue injury.

The Shwartzman reaction is an exaggerated form of a host response to microbes, which, under less extreme physiologic conditions, functions primarily to eliminate microbes and limit their spread. Although TNF is now known to be one of the principal cytokines involved in such host responses, TNF was first identified as a factor present in the plasma of LPS-treated animals that could cause hemorrhagic necrosis of tumors. Some of the anti-tumor action of TNF is mediated by direct tumor cell lysis, a process not well understood but believed to involve TNF binding to surface receptors on tumor cells, thereby initiating apoptotic cell death (see Chapter 18). Mostly, however, TNF induces tumor necrosis by causing a local Shwartzman-like reaction to occur in the tumor vascular bed. The basis for the selective effect on tumor blood vessels is not known, but tumor cells appear to release factors that increase the sensitivity of local endothelial cells to TNF. These tumor factors act like the first injection of LPS.

TNF is the product of a single gene located within the MHC on chromosome 6 in humans. In the mononuclear phagocyte, TNF is initially synthesized as a nonglycosylated transmembrane protein of approximately 25 kD. The orientation of membrane TNF is that of a type II membrane protein, i.e., the amino terminus is intracellular, the transmembrane segment is near the amino terminus, and the large carboxy terminus is extracellular. Membrane TNF assembles as a homotrimer; the interactions among subunits involve the extracellular carboxy terminal domains. A 17 kD fragment of each subunit, including the carboxy terminus, can be proteolytically cleaved off the plasma membrane of the mononuclear phagocyte to produce the "secreted" form, which circulates as a stable homotrimer of 51 kD. Native TNF assumes a triangular pyramidal shape such that each side of the pyramid is formed by a different monomeric subunit. The receptor binding sites are at the base

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